Neuroscience module

Lecture (5)

Neurotransmitters related to depression, gait disorders and anxiety

BY

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Lecture Key points

- Metabolism of neurotransmitters and related disorders

INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be

able to:

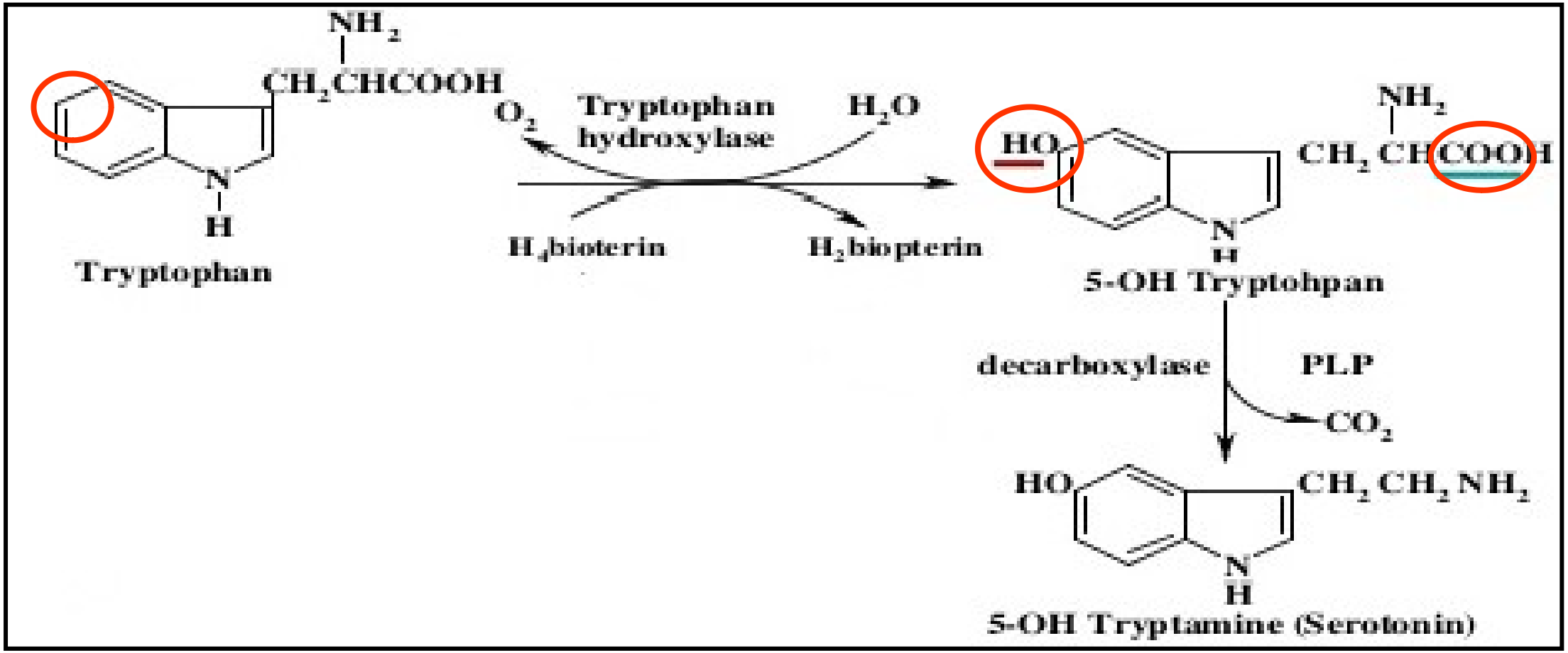
1. **Define neurotransmitter**
2. **Illustrate the major biochemical pathways for neurotransmitter synthesis and degradation.**
3. **Relate some clinical disorders to disruption of neurotransmitter metabolism like:**

- **Carcinoid tumor (argentaffinoma)**
- **Parkinson's Disease**
- **Pheochromocytoma**
- **Convulsions**

Neurotransmitters

Are the brain chemicals synthesized by nerve cells and communicate information throughout our brain and body cells

1) Biosynthesis of Serotonin



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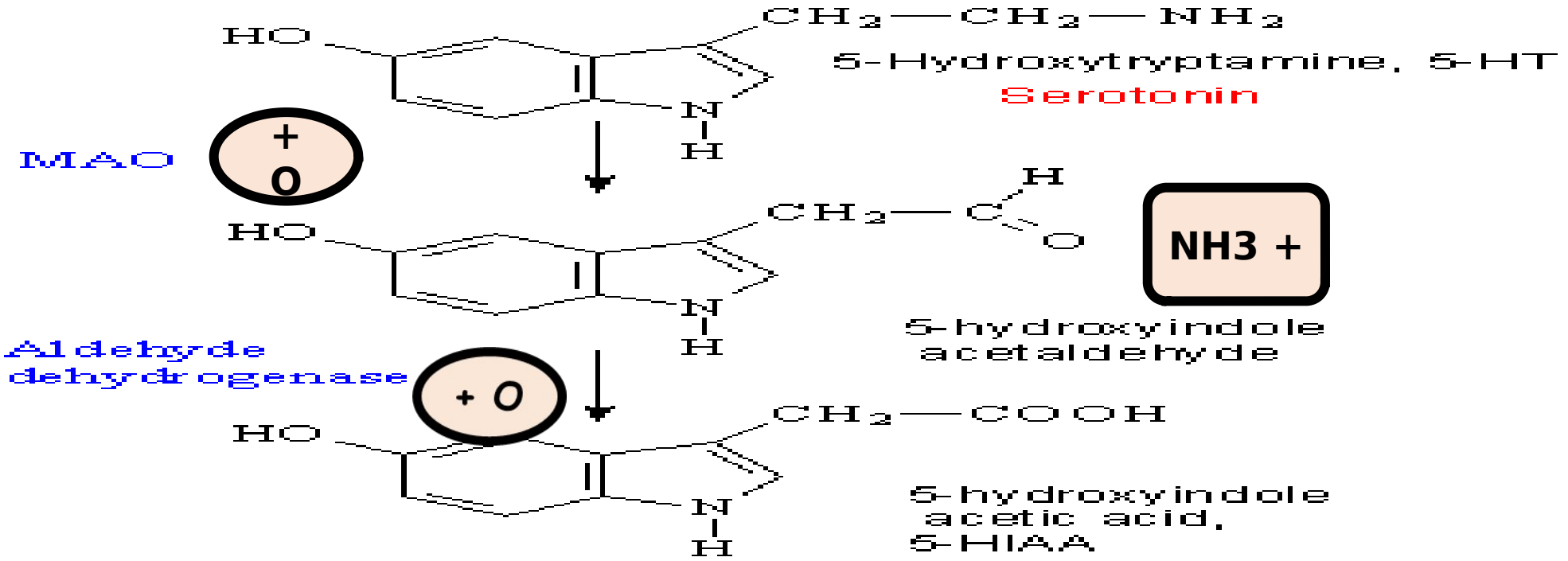
Degradation of Serotonin



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Serotonin Catabolism

Serotonin is degraded by monoamine oxidase enzyme (MAO) MAKE OXIDATIVE DEAMINATION producing 5-hydroxyindolacetic acid (5-HIAA).

Serotonin (5 hydroxytryptamine) functions

- Is a biologically active amine.

-Produced in:

*CNS

*Argentaffin cells of gastrointestinal tract

*Platelets.

Functions:

1- In CNS:

Acts as neurotransmitter.

a- Regulate pain perception

b- Regulation of sleep (relaxation) , reduce appetite

c- Cognitive functions (learning) and improve mood

(sense of well being & pleasure)

d- Source of melatonin in the pineal body.

2-Stimulates smooth muscle contraction

→ Vasoconstriction so regulate temperature and blood pressure

3-Important for GIT motility.

So deficiency causing insomnia, anxiety, weight gain, disability and depression

Clinical correlatio

1- *Carcinoid tumor* (*argentaffinoma*):

* **is a tumor of argentaffin cells of gastrointestinal tract**
* **characterized by:**
* **increase production of serotonin**
* **decrease production of nicotinic acid causing manifestations of pellagra**

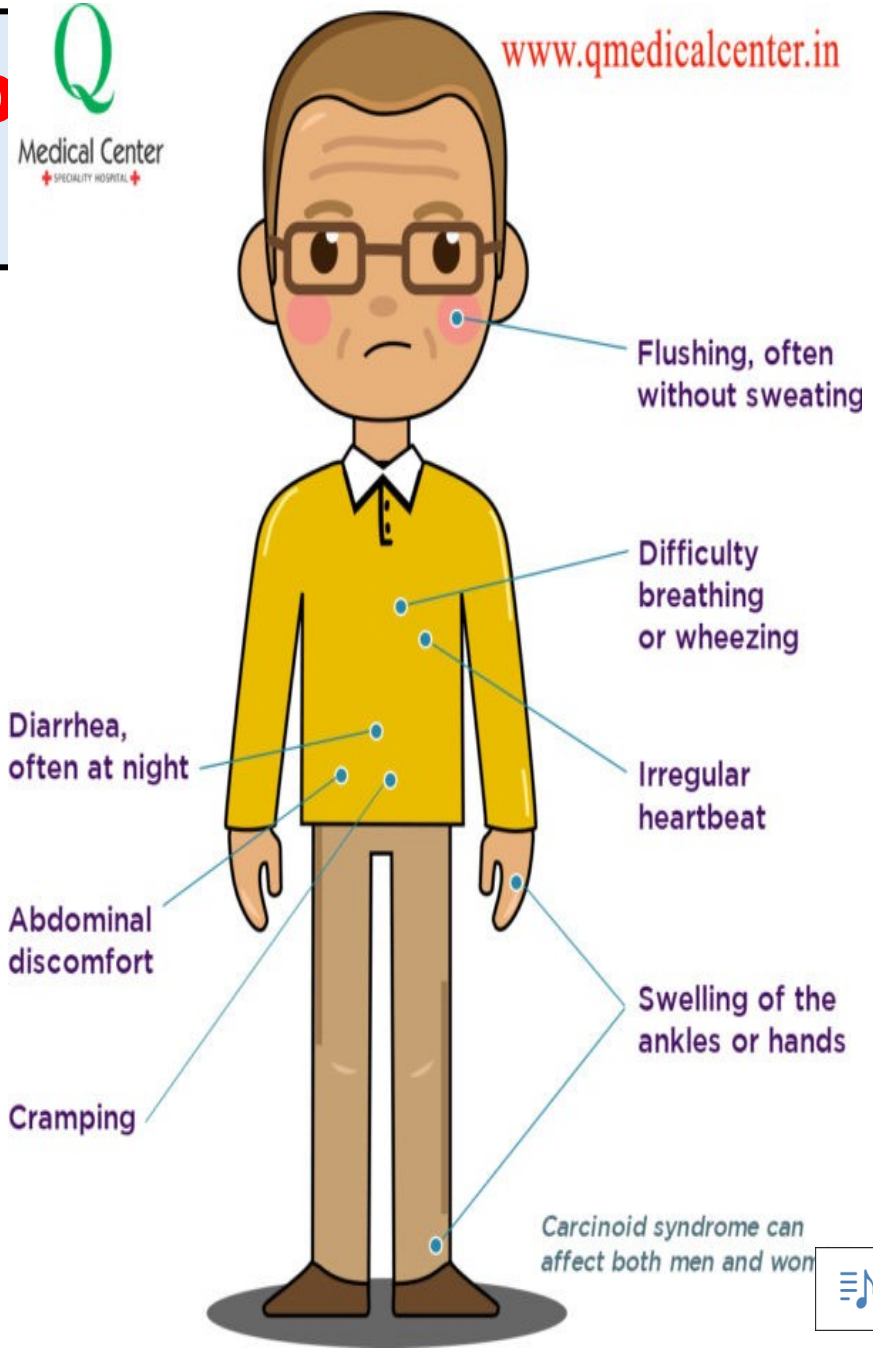
(Diarrhea-Dementia &Dermatitis)

* **and increase 5-HIAA in urine.**

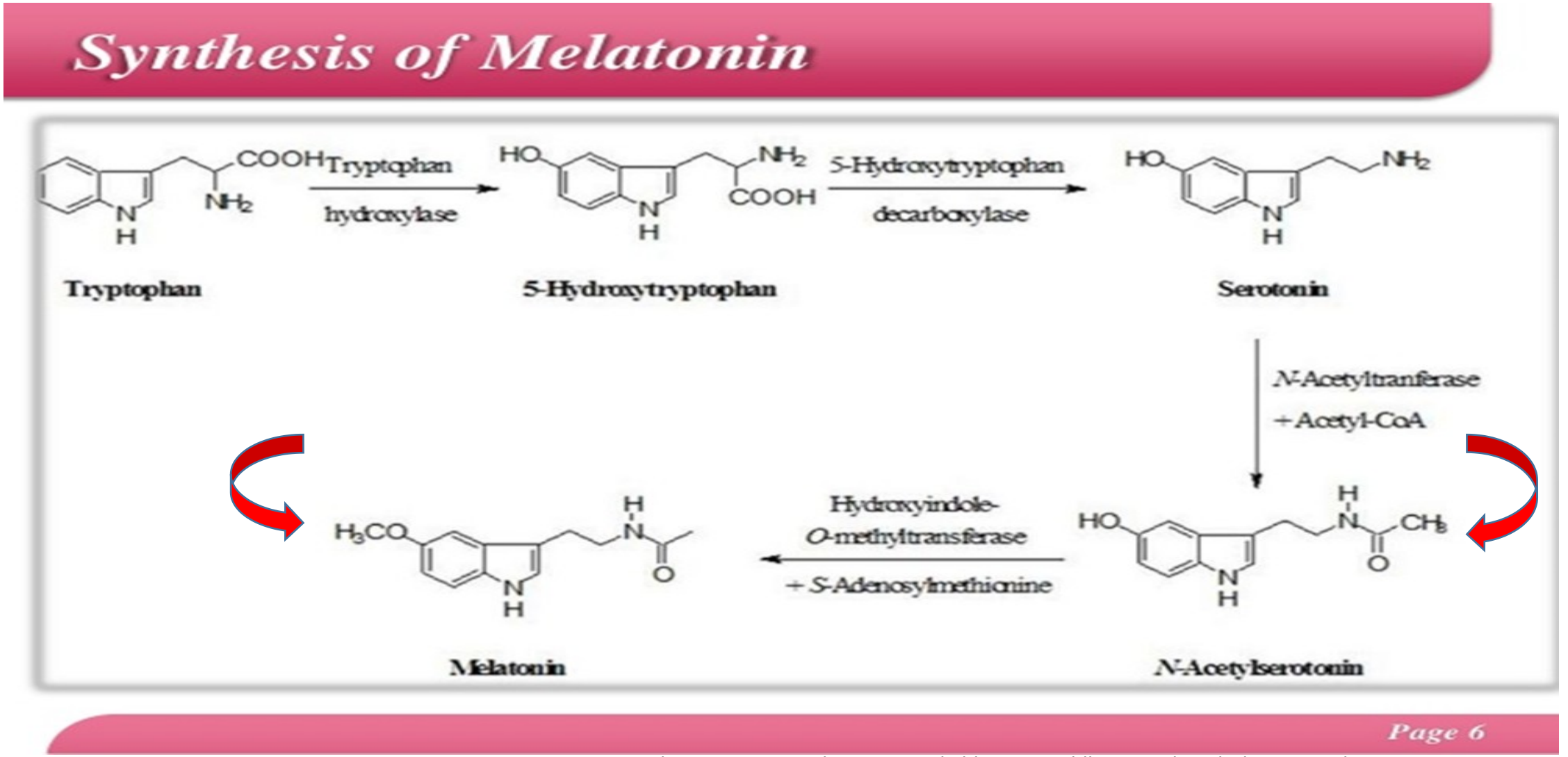
2-Selective serotonin reuptake inhibitors (SSRIs):

Maintain serotonin levels, thereby functioning as antidepressants

Like Cipralex



Melatonin



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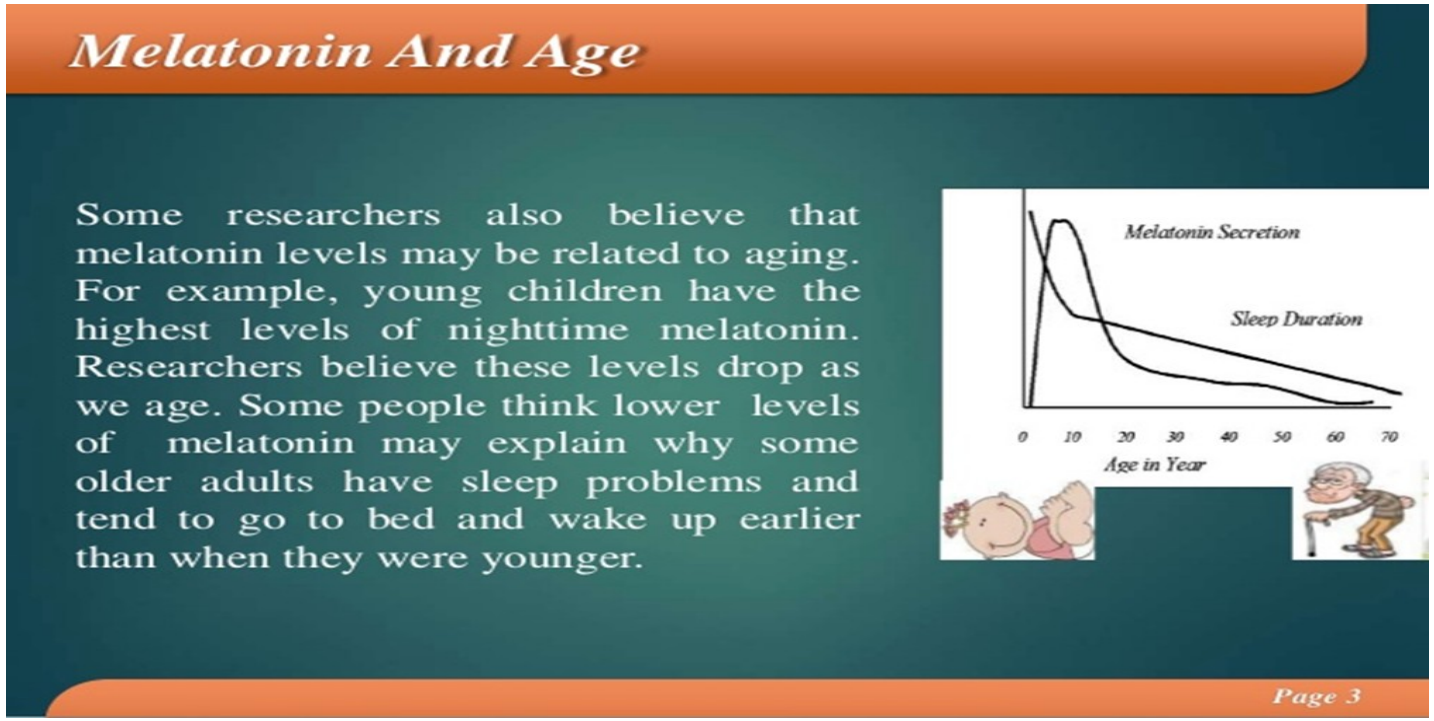
Melatonin Function

- Stimulate immune system

- Antioxidant protect against free radical

-Anticancer

- Its formation follows a circadian rhythm (diurnal variation); it is stimulated by dark and inhibited by light so regulate sleep cycle prevent insomnia so protect against Alzheimer


Melatonin And Age
Some researchers also believe that melatonin levels may be related to aging. For example, young children have the highest levels of nighttime melatonin. Researchers believe these levels drop as we age. Some people think lower levels of melatonin may explain why some older adults have sleep problems and tend to go to bed and wake up earlier than when they were younger.
Melatonin Secretion
Sleep Duration
0 10 20 30 40 50 60 70
Age in Year
Page 3

Melatonin deficiency

1. **Cigarettes**
2. **Caffeine**
3. **Frequent stress**
4. **Antidepressants**

All previous due to lack of *sleep*

Metabolism of neurotransmitters and related disorders (Quiz)

Serotonin (5HT): (True or false)

1- Is synthesized from tryptophan

2- Is found in platelets cells

3- Its degradative product is VMA

Answer:

1 (T)

2 (T)

3 (F)

2-Biologically active amines derived from phenylalanine and tyrosine:

Catecholamines

(Catechol means benzene ring with two hydroxyl side groups)_

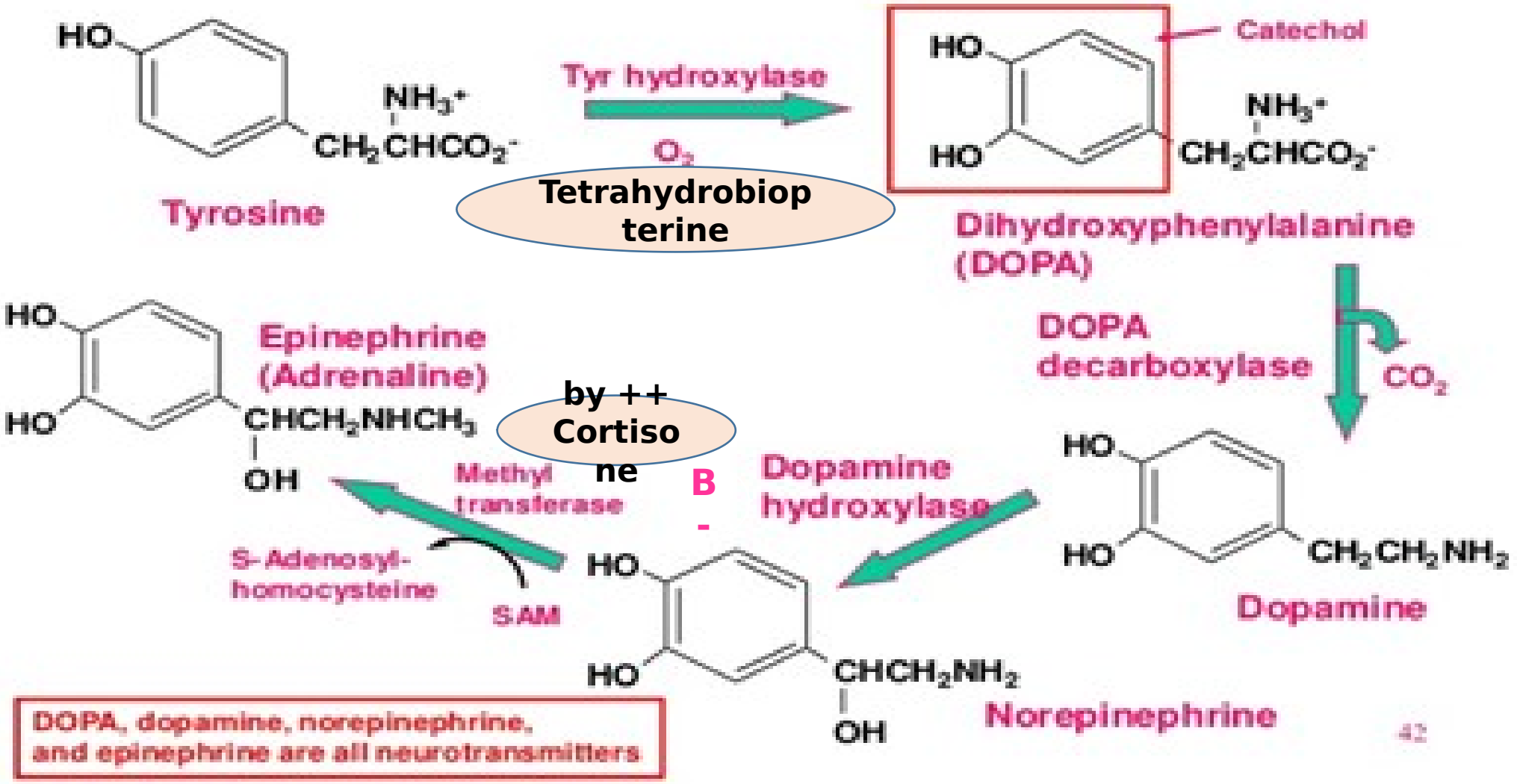
*** Dopamine, Epinephrine and Norepinephrine**

*** Are synthesized in the brain and adrenal medulla**

(Chromaffin cells or pheochromocytes)

*** Release of the hormones epinephrine and norepinephrine from the adrenal medulla of the adrenal glands is part of the fight-or-flight response**

Catecholamine Biosynthesis



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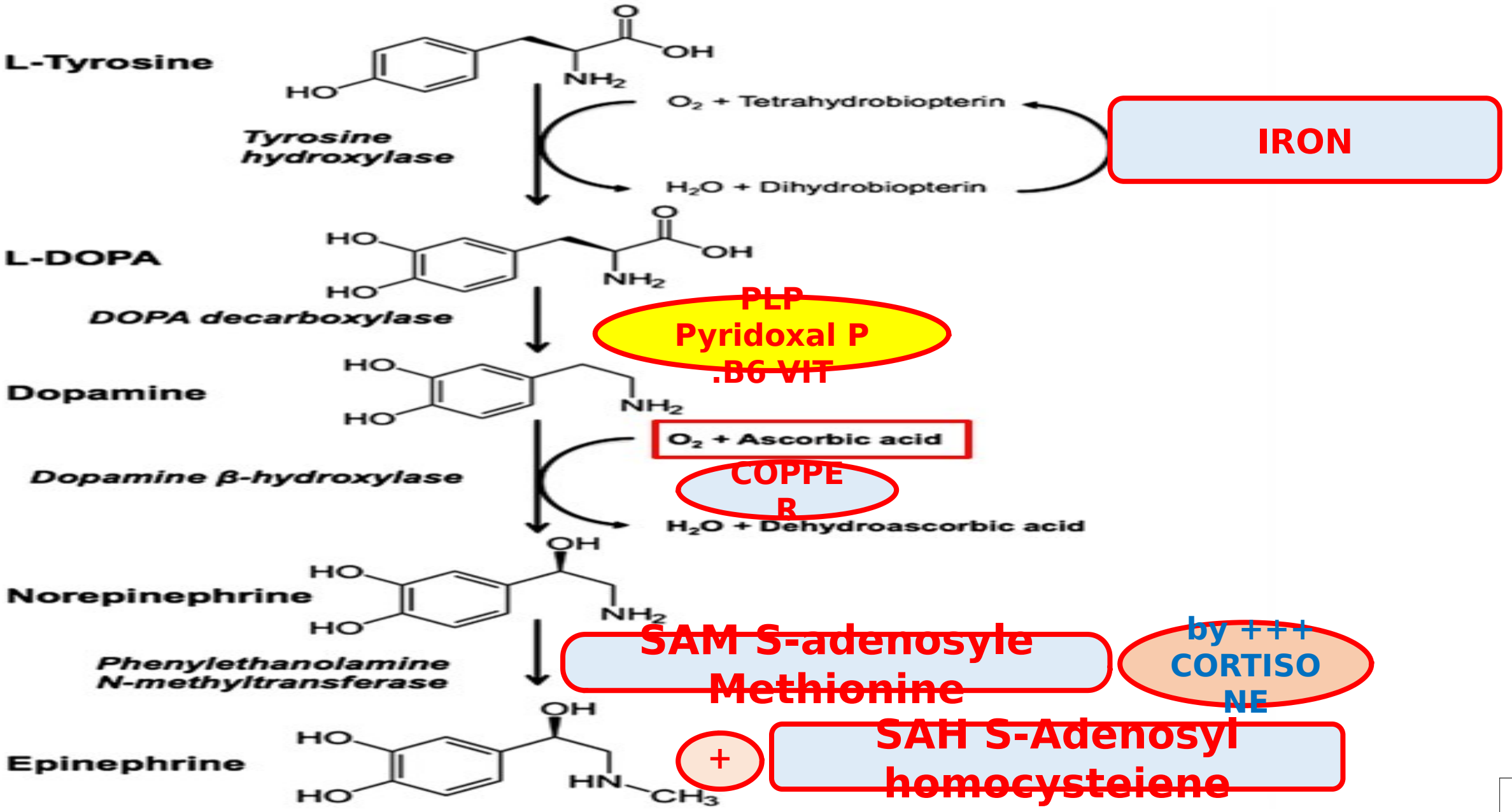
Vitamin C is required to synthesize catecholamines



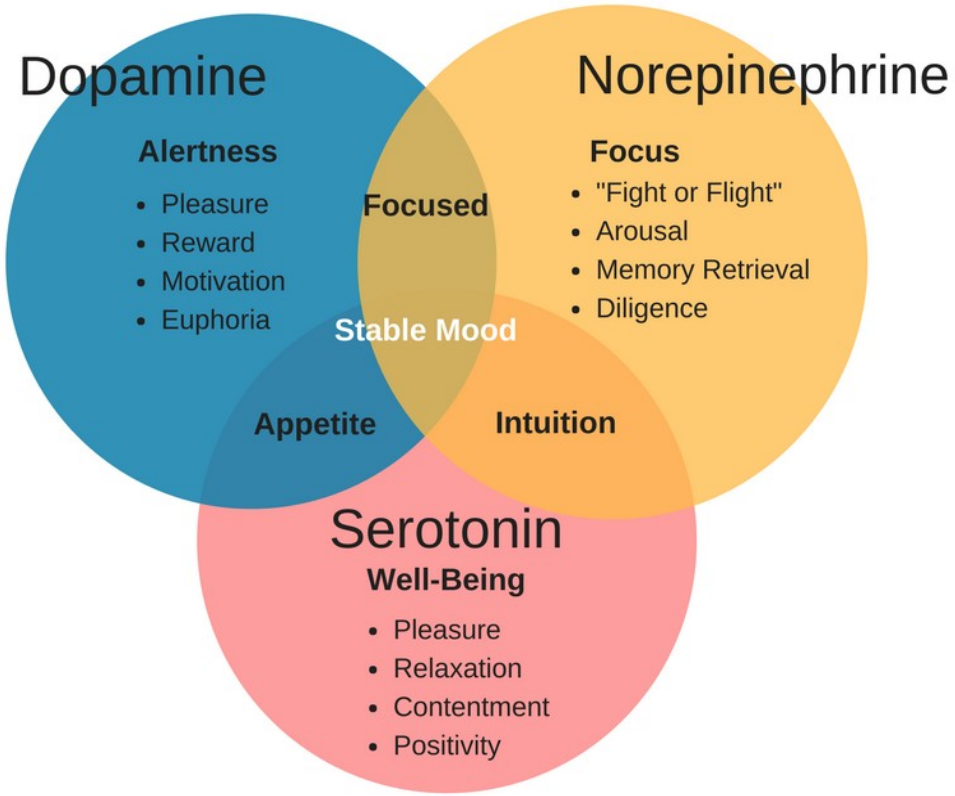
Zipursky JS et al. *BMJ Case Rep* 2014; PMID 24859547

The rate limiting enzyme in catecholamine synthesis is tyrosine hydroxylase which is inhibited by different catecholamines

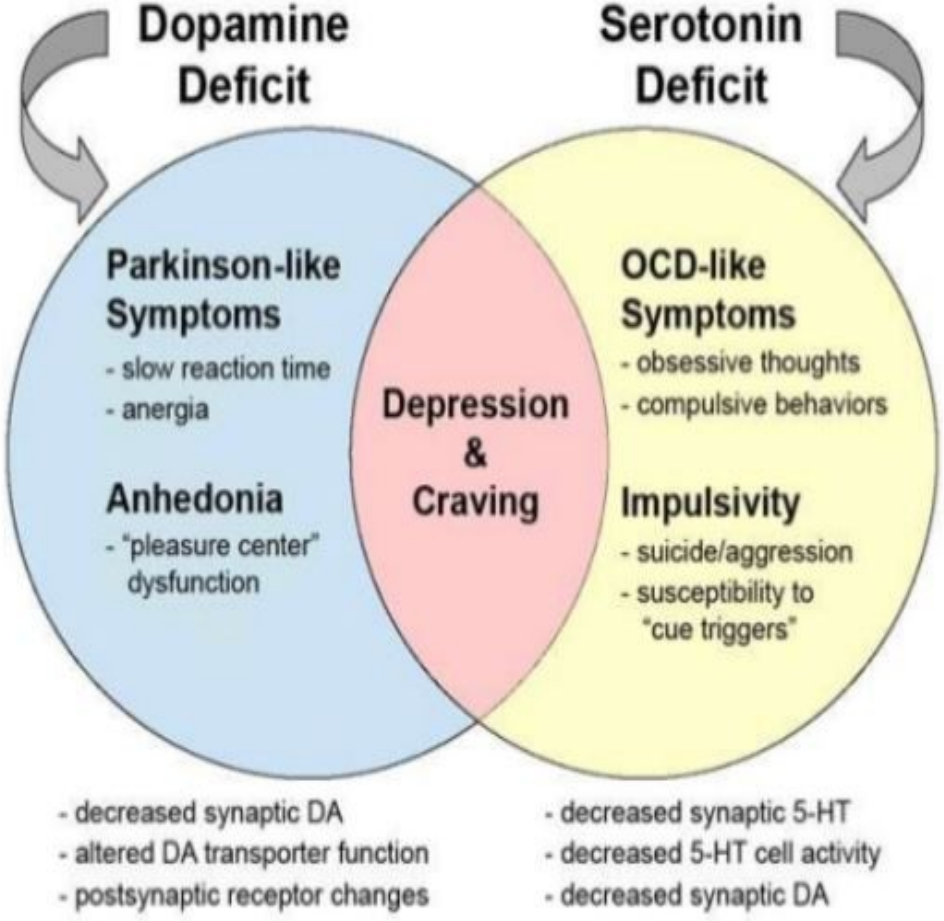
(-ve feedback)

- **The primary end product in medulla is NE in Newborn**
- **With advancing of age Epinephrine is dramatically raised this depends upon cortisol LEVEL which stimulate**
- **N-methyltransferase enzyme**

Function



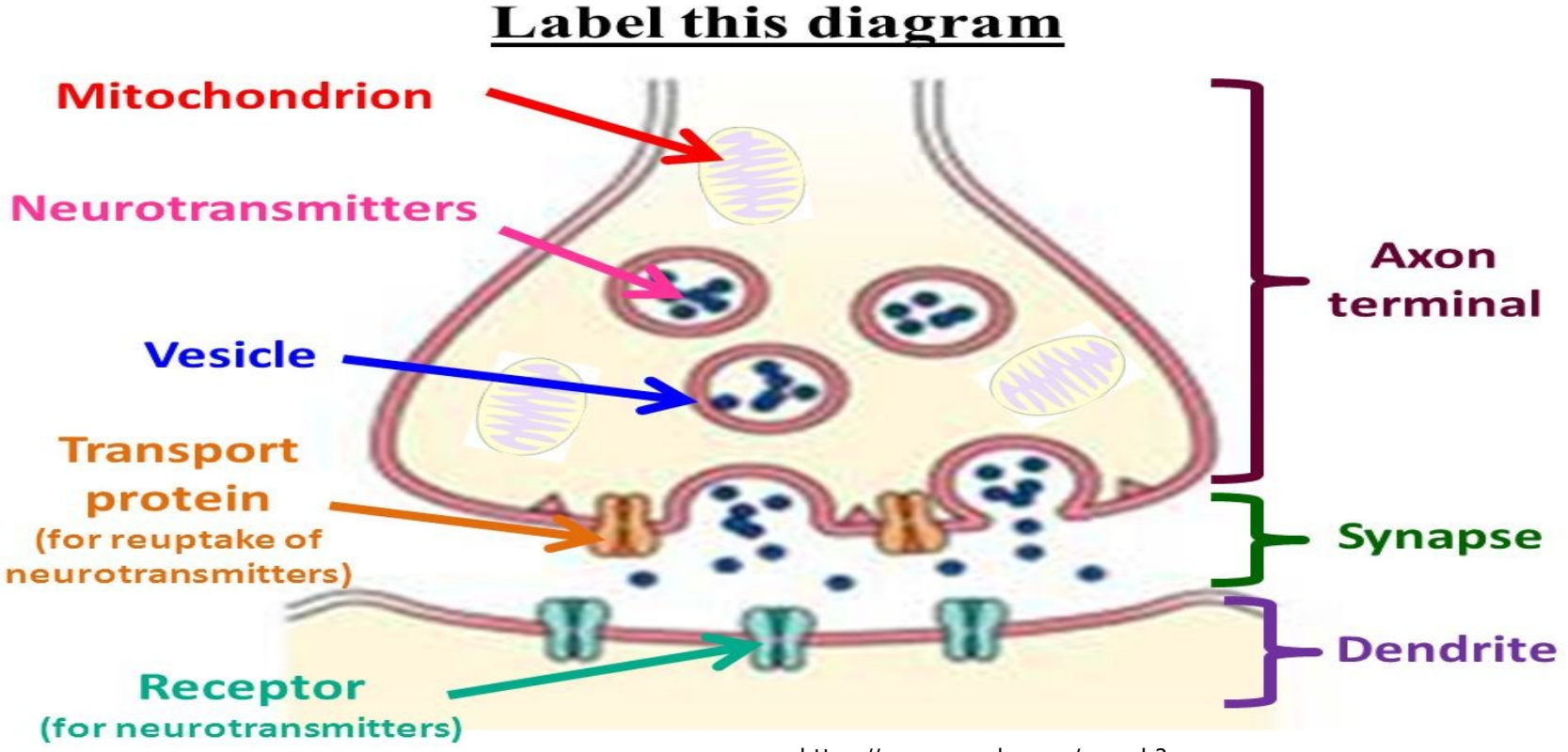
Deficiency



Fates of catecholamines

1- Active uptake by sympathetic nerve endings:

It is ... cat...



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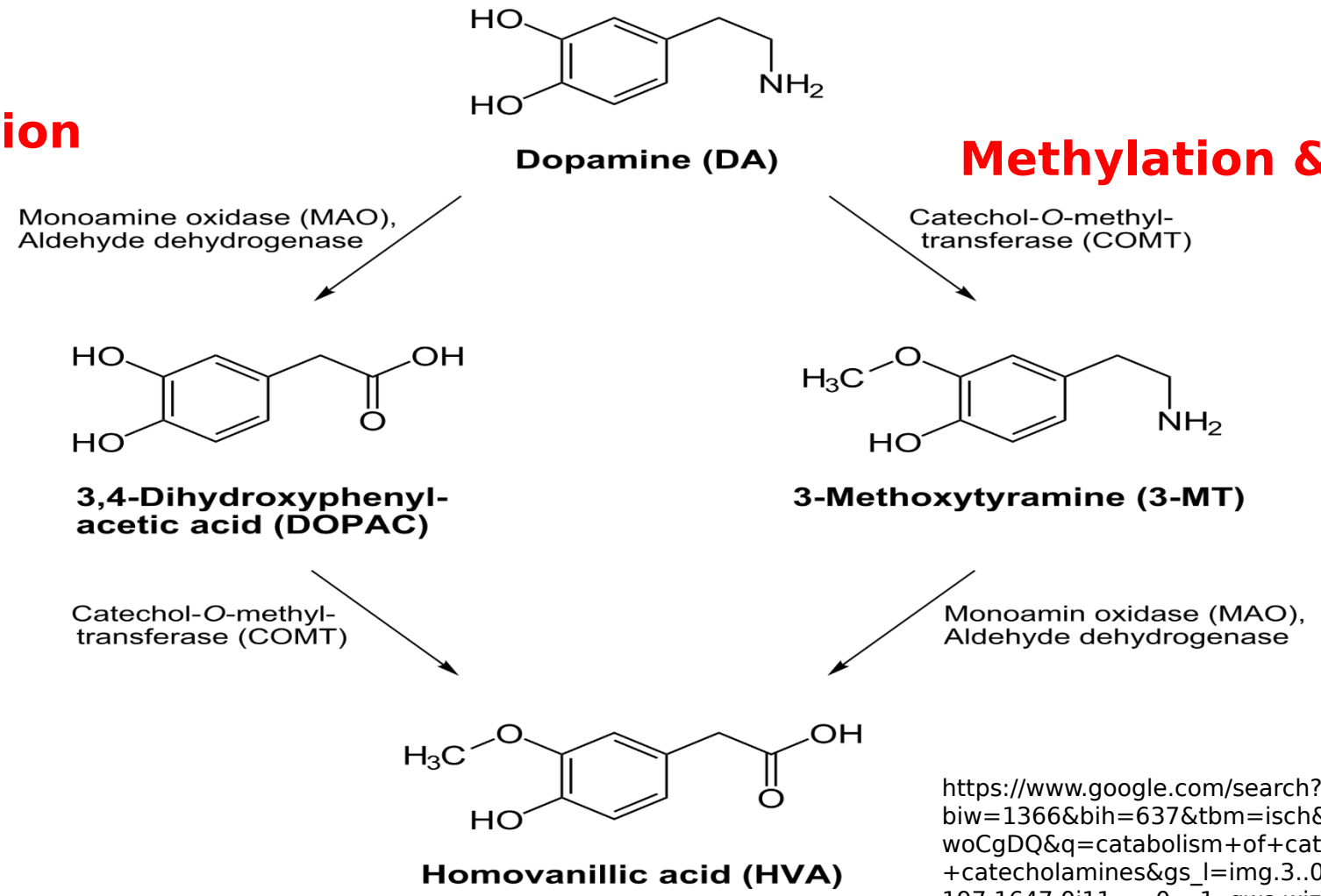
2- Catabolism to biologically inactive products:

A) Catabolism of dopamine

Oxidative Deamination Inactivation &



Methylation & inactivation

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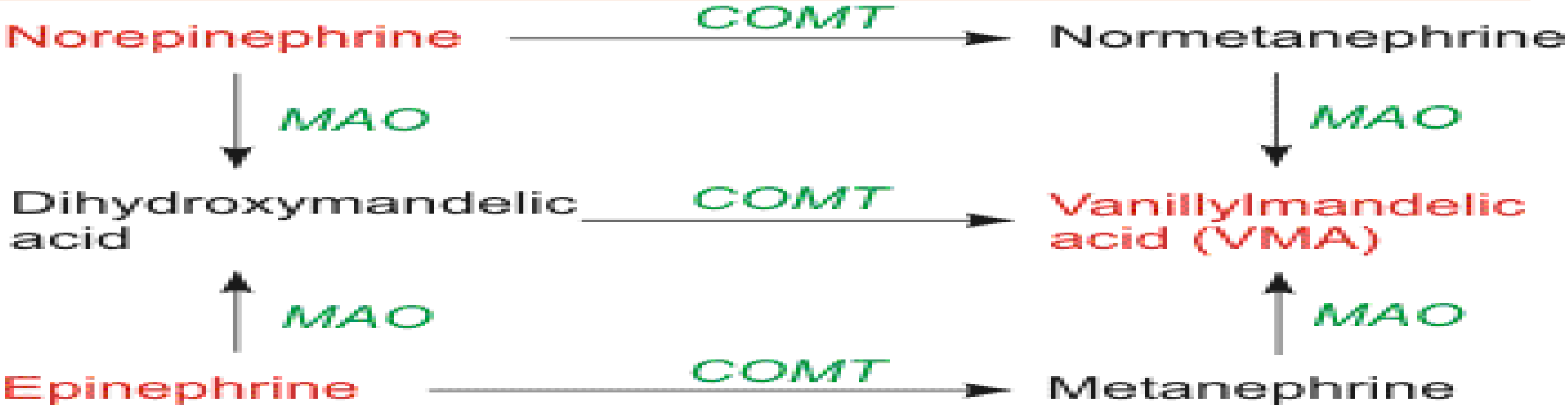
B) Catabolism of epinephrine and norepinephrine at adrenergic nerve endings

By MAO and COMT into Vanillylmandelic acid (VMA)

The metabolic end product



MAO = monoamine oxidase
COMT = catechol-O-methyltransferase

***VMA is detected in urine**

The normal level of VMA in urine is 5 mg/day and is increased up to 500 * .mg/day in Pheochromocytoma

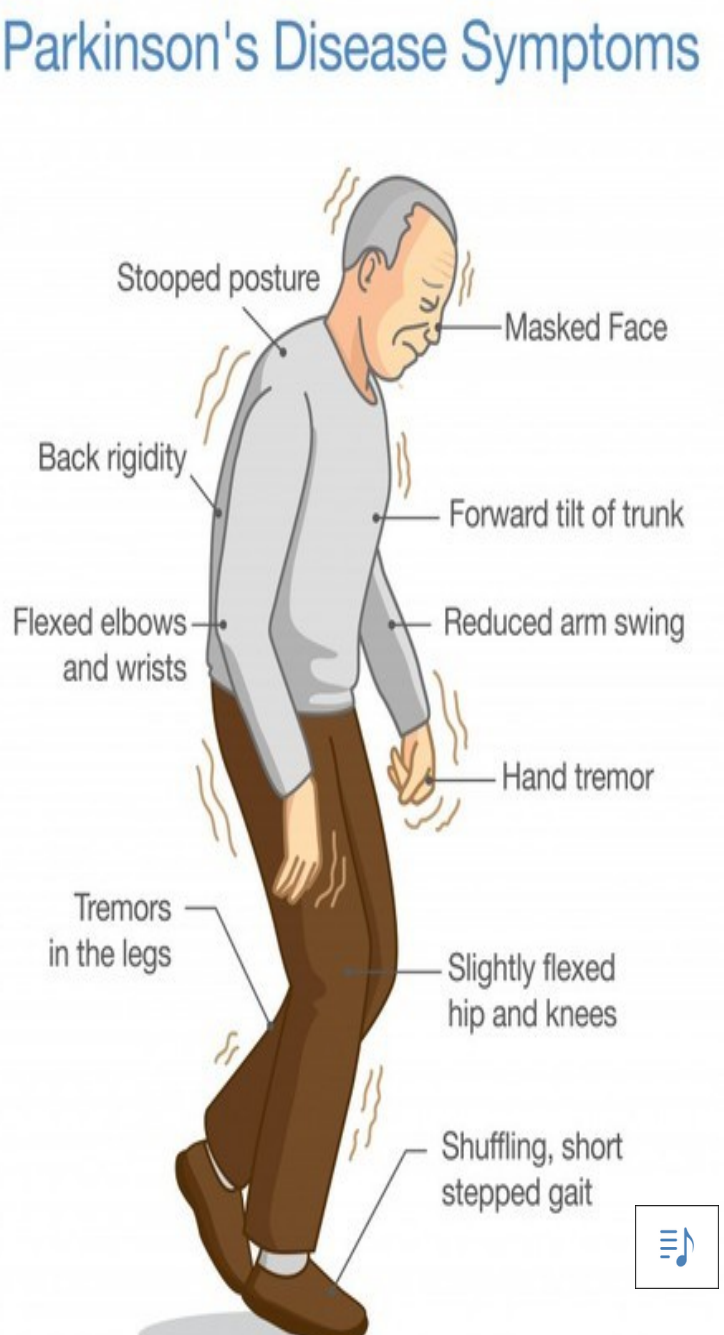
Clinical Considerati

1- Parkinson disease:

- A movement disorder, due to deficienc of Dopamine in the brain

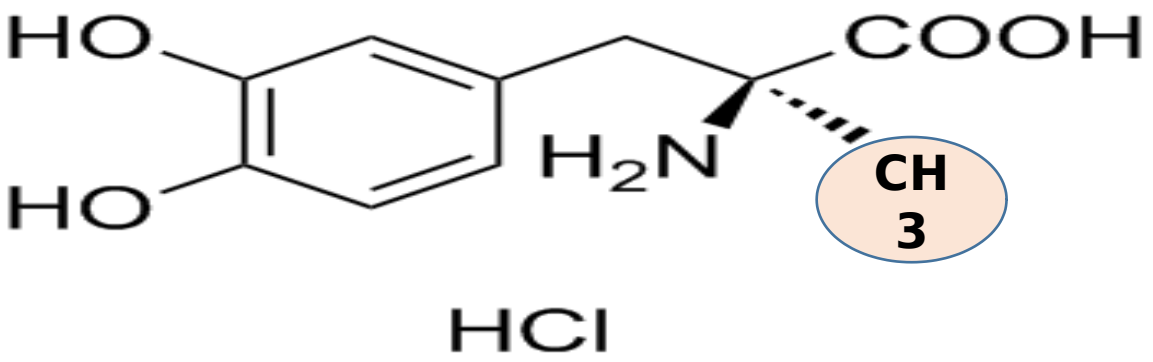
Treatment

- L-dopa (precursor of dopamine) is used in the treatment of parkinsonism as it can cross the blood brain barrier …. Dopamine cannot
- Also dopamine agonists LIKE PARLODEL
- COMT INHIBITOR & MAO INHIBITORS will increase dopamine concentration in brain via decreasing degradation



2. α-methyl dopa (Aldomet) :

Is used in the treatment of hypertension as it can competitively inhibit DOPA decarboxylase as it is structurally similar to D



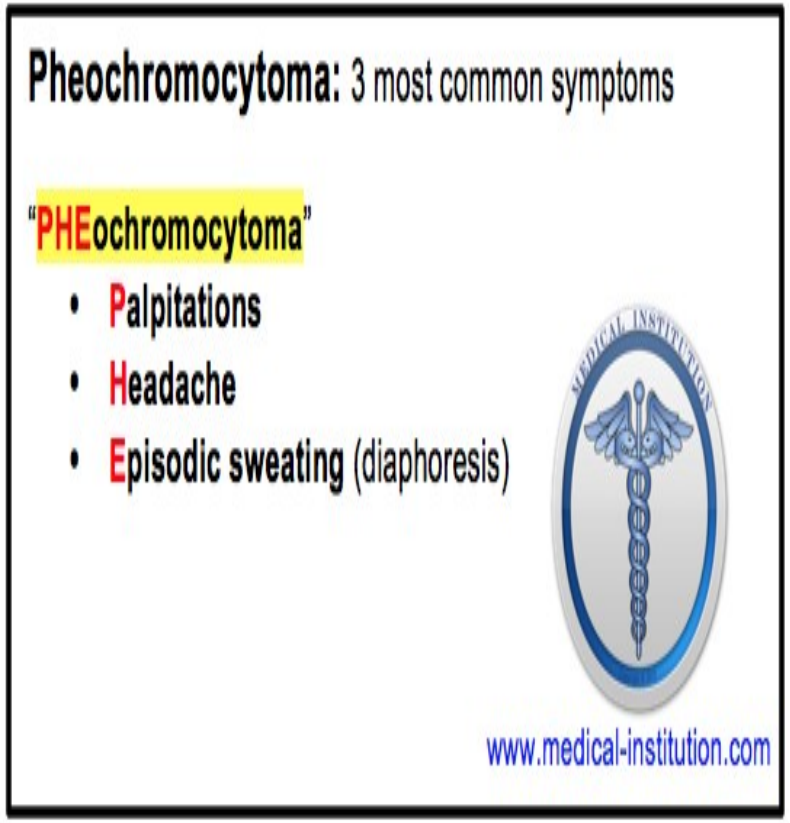
3. Pheochromocytoma:

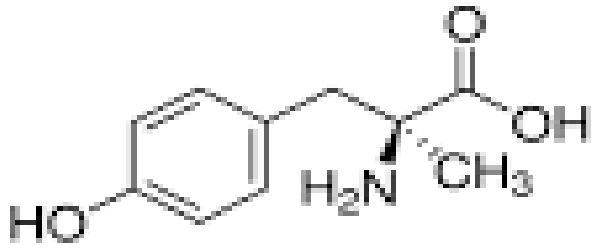
* A tumor of the chromaffine cells of adrenal medulla.

* It is manifested by excessive production of catecholamines→ sever refractory hypertension, palpitation repeated several times.

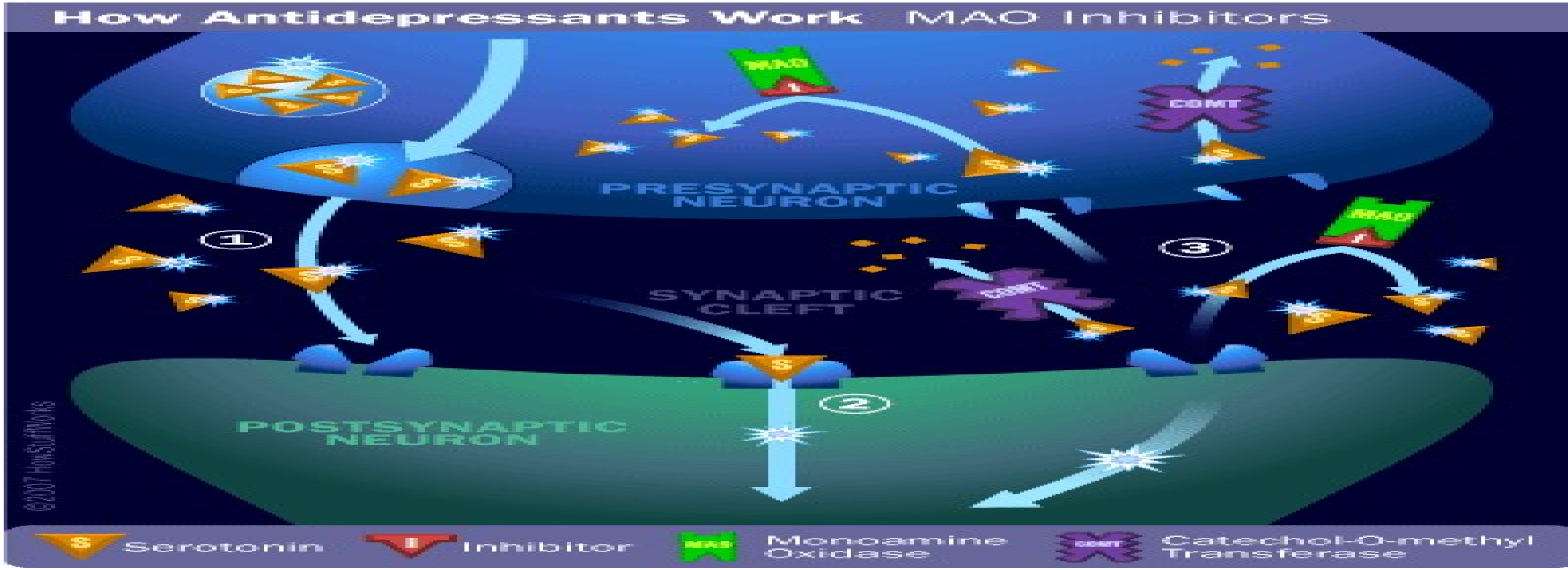
* With much increase in VMA LEVELS in urine

* Treated by α-methyl tyrosine which competes with tyrosine for tyrosine hydroxylase enzyme→ inhibition of catecholamine synthesis.





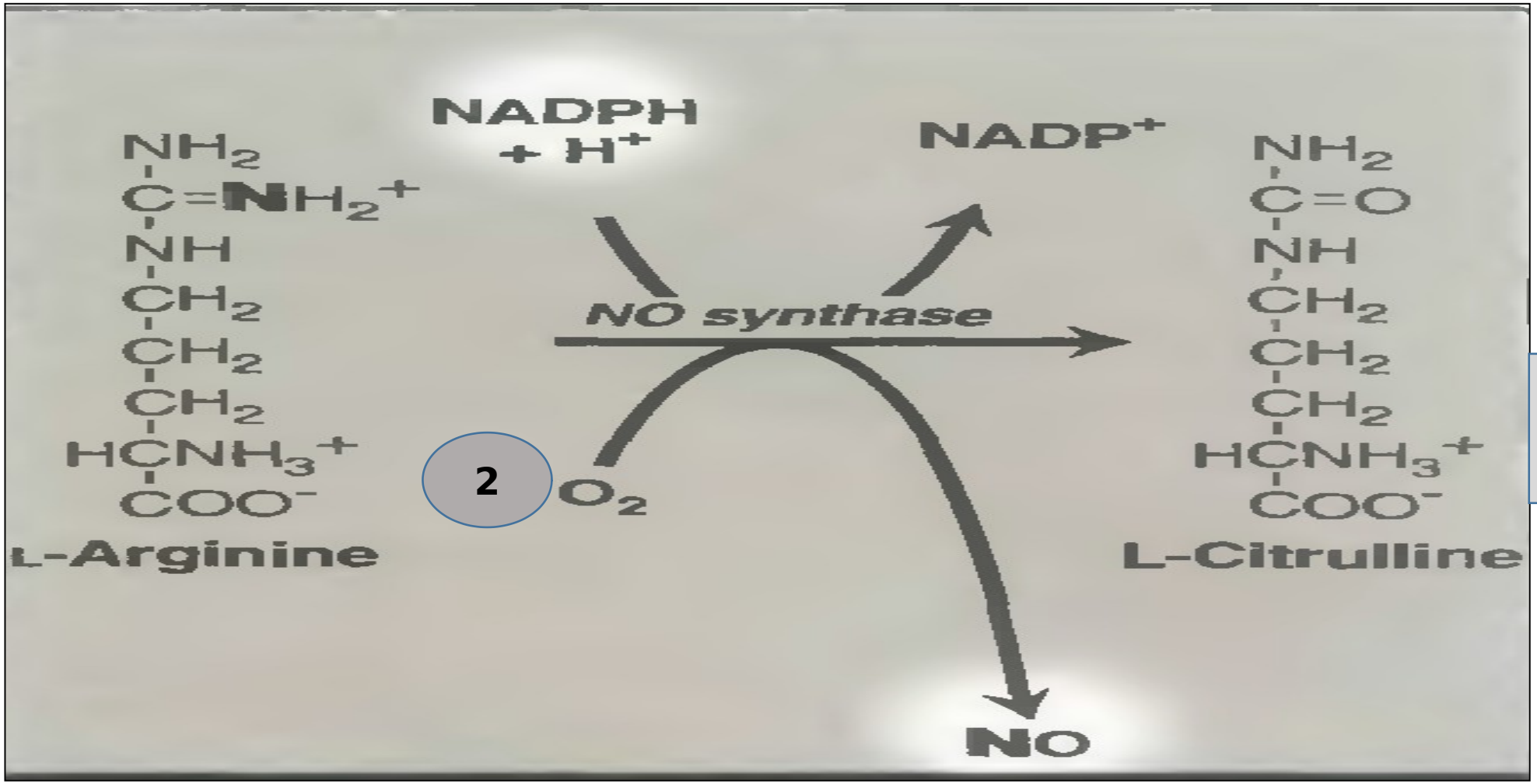
4. Monoamine oxidase inhibitors:



- **MAOIs inactivate the enzyme increase level of NE & Serotonin**

This is responsible for the antidepressant action of these drugs

Synthesis of nitric oxide (NO)



2 H2O

Lippincott's illustrated reviews in Biochemistry

Functions of NO:

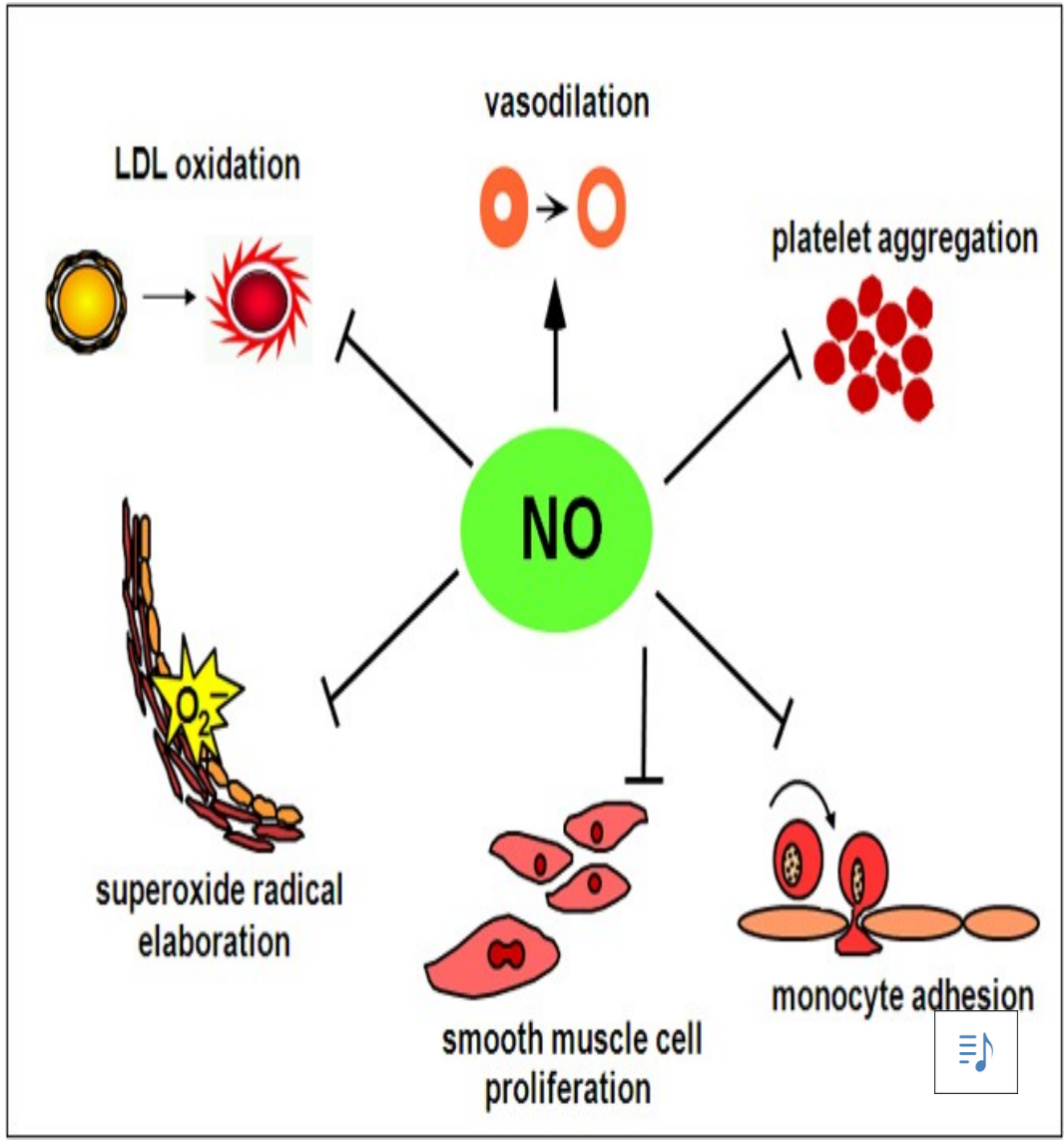
- Nitric Oxide is an endogenous protector of the vessel wall

-Is a potent vasodilator of cerebral, coronary and muscular arteries.

-It relaxes smooth muscles of GIT and urogenital tract so decreasing motility

-It stimulates release of hormones from hypothalamus.

-It is produced by



5- Pharmacological functions of NO:

Nitroglycerin(Dinitra) is used as tablet under -1 tongue to treat angina, it gives NO causes VD so lowers blood pressure

Inhalation of NO can be used in the -2 treatment of pulmonary hypertension and pulmonary edema via pulmonary Vasodilatation

Nitric Oxide

physiological, biochemical, pathological functions

Urogenital System

- Reninsecretion
- Penile erection
- Ferilization
- Spermatogenisis, oogenesis, ovulation

Cardiovascular System

- Vasodilation
- Microvascular tone regulation
- Leukocyte adhesion
- Platelet aggregation/inhibition
- Microvascular permeability

Respiratory System

- Bronchial dilation
- Pulmonary vascular reactivity
- Alveolar-capillary membrane permeability

Neurological System

- Learning
- Memory
- Neural protection
- Neuronal toxicity
- Neurotransmission
- Neuronal development
- Nociception

Immune System

- Innate immunity
- Cytotoxic chemical
- Cellular injury protection
- Superoxide radical quenching

Excretory System

- Glomerular filtration
- Renal vasodilation
- Renal endothelial function

Endocrine System

- Posterior pituitary hormones gonadotropin hypothalamic releasing factor

Vision

- Neurotransmitter within retina
- Regulation of retinal blood flow
- Visual transduction · Effector in photoreceptors
- Muscle tone in retinal and choroidal circulation

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SOURCES OF DATA: *J Geriatr Cardiology* 2011 Dec; 8(4):230–242; *Vision Res* 1996 36(18):2979–2994

Gamma Amino Butyric Acid (GABA)

Is an

inhibitory neurotransmitter

derived from glutamic acid

by

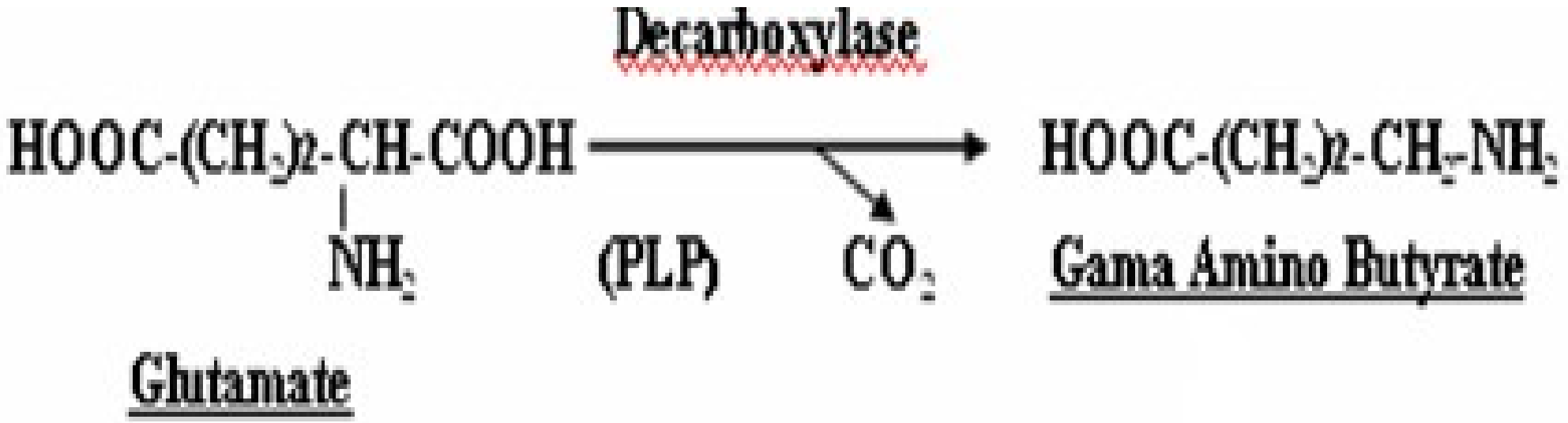
glutamic acid decarboxylase (GAD) enzyme

pyridoxal phosphate is required as a coenzyme

Gamma Aminobutyric Acid (GABA)

- GABA is the major inhibitory neurotransmitter of the brain.
- It turns off the functions of the neurons.
- It acts as a brake for the excitatory neurotransmitters that can cause anxiety.
- Without GABA, brain cells would fire uncontrollably (as in epileptic seizures).
- GABA deficiency is implicated in anxiety disorders, insomnia, and epilepsy.
- GABA excess is implicated in memory loss and inability for new learning.
- Agents that can block GABA-B receptors may improve learning and memory.

Synthesis of neurotransmitter (GABA)



Its level is reduced in brain in * Vitamin B6 deficiency with signs of hyperactivity and convulsions treated by Barbiturates (GABA AGONIST)

Metabolism of neurotransmitters and related disorders (Quiz)

A 56- year- old male presented with sever headache, palpitation, excessive sweating together with sever refractory hypertension repeated several times per week.

What investigation would you ask for to diagnose this case????

Metabolism of neurotransmitters and related disorders (Quiz)

A 43- year- old man presents to the emergency room with chest pain . His blood pressure was 220/150 mmHg. Which of the following compounds might lower his blood pressure

a. Melanin
b. Nitric oxide
c. GABA
d. Dopamine
e. Serotonin

Summary

1) *Biosynthesis & degradation of Serotonin*

Its relation to Depression & Carcinoid Tumor

2) *Biosynthesis & degradation of catecholamines*

Its relation to:

***Parkinson's disease**

***Hypertension & Pheochromocytoma**

***Depression**

3) *Biosynthesis of GABA ……. Convulsions*

Time for Students’ Questions

SUGGESTED TEXTBOOKS

- **Lippincott's illustrated reviews in Biochemistry by P.C. Champe, R.A. Harvey and D.R. Ferrier**
- **Fundamentals of Clinical Chemistry (Tietz)**
- **"Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin**
- **"Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell**

Thank You